Form). Thus, the applicants believe that the task of protein engineering is one of directing the changes to the *specific amino acids* responsible for binding or catalysis in order to improve protein function.

The studies available on the polypeptide growth factor hepatocyte growth factor/scatter factor (HGF) did not suggest that similar principles would not apply. Human HGF is a 728 residue protein which consists of six distinct domains: an N-terminal domain containing a hairpin loop structure spanning residues 70-96, four copies of a kringle domain, and a serine-proteinase homology domain. It also contains a long linker connecting the fourth kringle domain and the serine-proteinase homology domain which acts as an activation domain. Proteolytic cleavage at this site converts the single-chain precursor form of HGF (pro-HGF) into the two chain, active form.

As of the priority date of this application, the applicants believe that a number of mutagenesis studies had identified amino acids in HGF responsible for binding and activation of its cognate receptor, the product of the e-met protooncogene. For example, mutations of residue D117 in the N-terminal domain, or residues E159 and R197, in the kringle 1 domain, or V692 in the serine proteinase homology domain all affect receptor binding and activation and *decrease the activity* of HGF (Lokker et al (1992); Lokker et al (1994), both of record, see, PTO-1449 Form executed by the Examiner on June 18, 2002). Furthermore, as expected, these same documents showed that a number of other amino acid substitutions in the same domains have little or no effect on receptor binding and/or activation of HGF.

The amino acid substitutions which form the basis of the current invention *increase the activity* of HGF and achieve this result on two grounds:

(1) They target residues, such as R73 in the hairpin loop structure, which, as confirmed in subsequent studies (such as Lietha et al (2001)), copy attached and listed on the attached PTO-1449 Form, play a pivotal role in binding of HGF to heparan sulphate co-receptors.

(2) They introduce reverse-charge mutations at the relevant positions leading to a decrease in reaction on rates. This explains why changes of the same amino acids to non polar ones, such as alanine, as carried out in a number of separate studies (Lokker et al (1994) (of record); Sakata et al (1997) (of record); and Kinosaki et al (1998) (of record), had failed to produce HGF variants with increased biological activity.

In summary, the present specification describes both the key amino acid replacements required for enhancing the biological activity of HGF and the necessary reverse-charge nature of such mutations.

The applicants also believe that one of ordinary skill will appreciate from the specification (especially pages 9-12) that the described invention encompasses HGF variants having the claimed hairpin loop substitutions together with additional mutations in other domains of HGF. Not only is this specifically taught by the specification, but the ordinarily skilled person would have known from the prior art in the HGF field and from studies on protein structure and engineering in general (cited above), that the claimed hairpin loop mutations can be combined with other mutations within the HGF molecule.

The Section 112, first paragraph, rejections of claims 64-79 are traversed. Reconsideration and withdrawal of the rejection are requested in view of the following remarks.

The Examiner is urged to appreciate that a patent specification is a technical document addressed to a person of ordinary skill in the relevant art. A wide variety of

known HGF mutants were mentioned in the specification and many more have been described in the prior art. Hence, as of the priority date, the person of skill in the art knew of the existence and definition of mutants (or variants) of HGF. There was no suggestion in the prior art of any uncertainty over the meaning of identity of a mutant (or variant) of HGF. This was part of the common general knowledge of the ordinarily skilled person to whom the patent specification is addressed.

Claim 64 of the present application reads as follows:

> *A human hepatocyte growth factor (HGF) which is incapable of binding a heparan sulphate proteoglycan but which binds to the HGF receptor, wherein a positively-charged amino acid residue in the hairpin loop structure of wild-type human HGF, which structure is set forth in SEQ ID NO: 3, has been replaced with an amino acid with a negative charge.*

The claimed HGF molecules are defined as HGF molecules having at least one of the positively charged amino acid residues in the hairpin loop region replaced with an amino acid with a negative charge. The other residues in the hairpin loop region remain unchanged from the wild-type sequence (SEQ ID NO: 3) within this region. Thus the structural features defining the genus of the claimed HGF molecules are found in the description of the present application and in the pending claims.

The functional features of the claimed variant HGF molecules are also found in the description of the present application and in the pending claims.

The Examiner is understood to believe that the specification only describes, as a sequence outside of the hairpin loop structure, a single human polypeptide species of HGF. The applicants submit however that the present application describes, for example, at page 9, lines 7-9, that, in addition to the positive to negatively-charged

hairpin loop substitutions, the HGF molecules may be modified further. Numerous examples of these potential additional modifications are described on pages 9, 10, 11 and 12. For example, page 11 of the present application states that the claimed HGF molecules having the positive to negatively-charged hairpin loop mutations can be further modified to include the mutations present in the variant HGF molecules known in the art. Specifically, the additional mutations described in WO 92/05184, WO 96/40914, WO 93/23541, US 5,547,856, US 5,316,921 and US 5,580,963, which were incorporated by reference, and all of record, can be included in the claimed HGF molecules.

Other specific mutations which may be combined with the hairpin loop structure mutations, are alterations of residues H241, R242, K244 and R249 (page 10, lines 20-22) and alternations of an amino acid at or adjacent to any of amino acid positions 493, 494, 495 and 496 of wild-type human HGF sequence (page 11, lines 26-28).

The claimed HGF molecules define a genus to the extent that they contain additional mutations outside the hairpin loop structure. The specification describes a large number of additional mutations that may be present. Furthermore, as mentioned above, the ordinarily skilled person was well aware of many other additional mutations that might be included. In light of the teachings in the specification and the general knowledge of the skilled person relating to HGF mutants, there is a more than adequate written description of the invention as claimed.

The Examiner has specifically again refers Fiers v. Revel, 25 USPQ 2d 1601 (Fed. Cir. 1993), and to Univ. California v. Eli Lilly and Co., 43 USPQ 2d 1398 (Fed. Cir. 1997) as allegedly supporting his position. The applicants have previously provided an

analysis of each case on pages 12-17 of the Amendment dated April 9, 2004. The Examiner has not further commented, positively or negatively, on the applicants previous analysis of the case law as it may apply to the facts of the present case. The Examiner is requested to provide further comments in response for clarity of the record.

The Examiner has not made a further reference in the Office Action of August 5, 2004, to Fiddes v. Baird 30 USPQ 2d 1481 (BAPI 1993) (see, pages 4-5 of the Office Action dated January 9, 2004) such that perhaps the Examiner is in agreement with the applicants analysis of the case applied to the present facts found on pages 15-16 of the Amendment filed April 19, 2004.

Beyond the comments on pages 10-12 of the Amendment dated April 9, 2004, relating to the Examiner's previous reliance on Example 13 of the Revised Interim Utility Guidelines consideration of the following is also requested.

The facts and circumstances of Example 13 are submitted to be quite different from those of the presently disclosed and claimed invention.

Firstly, in Example 13, the isolated protein of SEQ ID NO: 3 is itself novel. By contrast, prior to May 1997, not only was human HGF known, a large variety of HGF mutants had been disclosed in the prior art. Thus, the skilled person was already aware of what constituted a variant HGF and how to identify them. Secondly, the presently claimed HGF molecules are defined by having at least one of the positively-charged amino acid residues in the hairpin loop structure replaced with an amino acid with a negative charge. The other residues in the hairpin loop region remain unchanged from the wild-type sequence (SEQ ID NO: 3) within this region. Thus, contrary to the situation in Example 13, structural features distinguishing the claimed molecules from

other compounds in the protein class are present in the disclosure and claims of the present application. Finally, pages 9-12 of the present application describe a large number of additional mutations that can be included in the claimed HGF molecule. This is in contrast to Example 13 in which the hypothetical specification does not provide any guidance as to what changes should be made. Since the facts in the present case are materially different from those in Example 13, any rejection under the written description requirement based upon the reasoning in Example 13 is submitted to be inappropriate.

The claims are submitted to be supported by an adequate written description.

Page 9, lines 7-9, for example, states that, in addition to the positive to negatively-charged hairpin loop mutations, the same HGF molecules may be modified further. A large number of examples of specific mutations which are contemplated are given in the specification on pages 9-12. Thus, the claims are submitted to not introduce new matter.

The Examiner is understood to rely on Rudinger (1976) in an attempt to support to Examiner's enablement rejection. The Rudinger reference is however submitted to be misleading in the context of the claimed invention. Firstly, as of May 1997, the conclusions of Rudinger were over twenty years out-of-date, and the science of protein engineering had advanced significantly since 1976. Since the experiments described by Rudinger required chemical modification of individual amino acid side-chains, it is no wonder that experiments to determine the significance of particular amino acids were considered to be "painstaking". However, particularly with the advent of modern molecular biology, experiments that may once have required such painstaking study could be performed much more rapidly and efficiently.

Furthermore, Rudinger only addresses the activity of peptide hormones; this is clearly evident throughout the document, from the title through to the conclusions. All of Rudinger's examples refer to peptide hormones of only eight or nine residues in length. This is completely different from larger proteins such as HGF which contains over 700 residues. *A priori*, therefore, the conclusions of Rudinger are submitted to not be relevant to the enablement of the presently claimed invention.

The claims are submitted to be supported by an enabling disclosure.

For completeness, the applicants note that the USPTO has previously granted claims directed to variants of HGF, which do not recite a base sequence for wild-type HGF. For example, claim 1 of U.S. Patent No. 5,328,837 reads:

> *"An isolated nucleotide molecule encoding a hepatocyte growth factor (HGF) variant having an amino acid alternation at a site within the protease domain of HGF, said variant retaining substantially full receptor binding affinity of the corresponding wild-type HGF and being substantially devoid of HGF biological activity."*

Claim 1 of U.S. Patent No. 5,879,910, reads:

> *A hepatocyte growth factor (HGF) variant comprising an amino acid alteration at or adjacent to position 692 of the wild-type human HGF (huHGF) amino acid sequence.*

Neither U.S. Patent No. 5,328,837 not 5,879,910 specify a base structure for HGF in the claims. These claimed molecules are available in the art and form a basis for demonstrating the generally advanced level of skill in the present art. Both these patents encompass and teach and describe HGF molecules having the specified mutations as well as additional unspecified mutations. Thus, the USPTO has previously found that claims to specific variants of HGF which do not specify a base structure for

the protein *meet the requirements for patentability*. The present Examiner's appear to be contrary to the level of skill in the art which has been previously confirmed by the Patent Office. If the USPTO maintains its objections on these grounds of lack of written description and enablement, it is understood to be a *de facto* admission that it should not have granted at least the noted claims of U.S. Patent Nos. 5,328,837 and 5,879,910. Such a contrary suggestion regarding the validity of a U.S. patent claim by the Examiner is contrary to MPEP § 1701. The Examiner is requested to provide, pursuant to 37 CFR 1.104(d)(2), any further information regarding the validity of the noted claims.

The claims are submitted to be supported by an adequate written description which teaches how to make and use the claimed invention. Withdrawal of the Section 112, first paragraph, rejections of the claims are requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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